

## REMARKS

### I. Status of the Claims

With entry of this amendment, claims 45-67, 69, and 81-87 are pending in this application. Claims 45-67, 69-76 and 81-87 are rejected. Claims 77-80 are withdrawn. Claim 89 is new.

Applicants wish to thank the Examiner for withdrawing the previous rejections under 35 U.S.C. 112, 102(b) and 102(e). Office Action, page 10.

Solely to advance prosecution and without disclaimer of or prejudice to the subject matter recited therein, claims 45, 46, 50, 51, 55, 56, and 60 are amended to more particularly describe the subject matter of the invention. Support for “[a] method of assaying a sample . . . wherein the presence, concentration, or activity of said enzyme or said factor is not known” of claims 45, 46, 50, 55, 56, and 60 may be found, for example, in the specification at page 5, lines 1-25. Support for “[t]he method . . . wherein said enzyme catalyzes formation of a covalent bond between said first substrate and said second substrate” of claim 51, may be found, for example, at pages 16, line 27 to page 17, line 1.

Solely to advance prosecution and without disclaimer of or prejudice to the subject matter recited therein, claims 85 and 86 are amended and claim 89 is added to more particularly describe the subject matter of the invention. Support for “[t]he method . . . wherein said electrode is not a carbon electrode” of claim 89 may be found, for example, in the specification at page 14, lines 2-3.

The amendments introduce no new matter.

## II. The Markush Group is Proper

The Examiner has objected to claims 54, 64, 66, 83-84, and 87 as “recit[ing] an improper Markush group.” Office Action, page 2. The phrase “chosen from” has been rejected as being in improper Markush format.

However, Applicants point out that “selected from the group consisting of” is not the only acceptable alternative language format. MPEP § 2173.05(h) states the proper test: “Alternative expressions are permitted if they present no uncertainty or ambiguity with respect to the question of scope or clarity of the claims.” The guidance for examination continues: “One acceptable form of alternative expression, which is commonly referred to as a Markush group, recites members as being ‘selected from the group consisting of A, B and C.’ “ MPEP § 2173.05(h)(I), *citing Ex parte Markush*, 1925 C.D. 126 (Comm’r Pat. 1925) (emphasis added). Other examples of acceptable alternative claim language published by the PTO may be found in the following sources: MPEP Appendix AI (PCT), Example 20, p. AI-44 of the July 1998 edition (“wherein R1 is methyl or phenyl, X and Z are selected from oxygen (O) and sulfur (S).”); *Training Materials For Examining Patent Applications with Respect to 35 U.S.C. Section 112, First Paragraph - Enablement Chemical/Biotechnical Applications*, released August, 1996 (“X selected from A, B, and C”). In sum, the PTO expects and allows alternative claim language other than the strict formulation “selected from the group consisting of,” and provides a test for determining proper alternative claim language.

Applying the proper test to Applicants’ claim language, no uncertainty or ambiguity is found. For example, in claim 54, Applicants claim that, said enzyme is selected from nucleic acid polymerases, nucleic acid ligases, integrases, ribosomes, ubiquitin-protein ligases and trans-glutaminases. Thus, said enzyme is a nucleic acid

polymerase, nucleic acid ligase, integrase, ribosome, ubiquitin-protein ligase or transglutaminase, respectively. Applicants find “no uncertainty or ambiguity with respect to the question of scope or clarity” of this claim language.

Therefore, this objection should be withdrawn.

### **III. The Claims Are Definite**

The Examiner rejects claim 51 under 35 U.S.C. § 112, second paragraph, “as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.” Office Action, pages 2-3. According to the Examiner, the “enzyme forms a covalent bond” in claim 51 is “indefinite and unclear because it is not clear whether the enzyme forms a covalent bond with the first substrate or the second substrate or both or with the luminescence label.” Applicants disagree. However, solely to advance prosecution and without disclaimer of or prejudice to the subject matter recited therein, Applicants amend claim 51 to recite “[t]he method of claim 45, 46, or 50, wherein said enzyme catalyzes formation of a covalent bond between said first substrate and said second substrate.”

### **IV. Claim Interpretation**

The Examiner interprets “[t]he enzyme that modifies the rate of joining a first substrate with a second substrate” broadly as a DNA polymerase. Office Action, page 3. Applicants understand this statement to mean that according to the Examiner’s claim interpretation DNA polymerases are within the class of enzymes assayed in the claimed method but the class of enzymes that may be assayed for in the method is broader and not limited to DNA polymerases. The specification clearly discloses joining enzymes such as, for example, polymerases, integrases, recombinases, and ligases. Pages 17

and 31. Consequently, Applicants request the Examiner's confirmation of the interpretation of the joining enzyme.

## **V. The Claims Are Not Obvious**

### **A. Rejection over Comb and Massey**

The Examiner rejects claims 45-54, 69, 81-82, 85, and 86-87 under 35 U.S.C. § 103(a) as allegedly being obvious over Comb in view of Massey. Office Action, pages 3-7. The Examiner alleges that Comb teaches "a method for assaying a sample for enzyme activity (DNA polymerase) that modifies the rate of joining a first substrate (DNA fragment of M13mp18 DNA) with a second substrate (complementary DNA fragment of M13mp18 DNA) to form a product (amplification product)" *Id.* at 4. Moreover, the Examiner states that Massey teaches the use of a luminescent label on an electrode . . . for the purpose of enhancing the efficiency of detecting the enzyme activity in said sample." Office Action, page 6.

Solely to advance prosecution and without disclaimer of or prejudice to the subject matter recited therein, Claims 45, 46, 50, 51, 55, 56, and 60 are amended to more particularly describe the subject matter of the invention, claiming "[a] method of assaying a sample . . . wherein the presence, concentration, or activity of said enzyme or said factor is not known."

Comb describes the characterization of a recombinant thermostable DNA polymerase. It does not, however, describe assaying a sample for an enzyme, where it is not known whether the enzyme is present in the sample or at what concentration or activity. Comb determined the specific activity of the polymerase, affirmatively added it to a reaction solution, and used it in biochemical reactions as defined by these units.

See, for example, col. 25, lines 45-46, table 1, and table 2. In fact, Comb specified the complete composition of the reactions and the only unknown was how Comb's polymerase would compare with other known polymerases. Comb, unlike the present invention, does not teach a method of assaying a sample for an enzyme. Thus, Comb is missing a key element of the claims.

In addition, Comb characterized the enzyme by using well-known techniques. See, for example, Examples VIII and IX. Comb did not teach nor even remotely suggest the use of any other method for assaying this enzyme, including the use of a luminescence assay to measure the product. Moreover, Comb compared the enzyme to other "well-characterized" enzymes. See, col. 30, lines 10-16. One skilled in the art would recognize that if one wants to characterize a novel enzyme and compare it with other well-characterized enzymes, that person would use techniques shown to produce the expected results, not use a novel technique. That simply was not the purpose of the experiments in Comb. Thus, Comb teaches away from using other techniques for measuring enzyme activity including a luminescence assay.

Moreover, Massey does not teach or suggest the use of a luminescence assay to assay a sample for a joining enzyme. Thus, there is not the slightest suggestion or motivation to combine Comb with Massey.

Furthermore, neither reference identifies any disadvantages or deficiencies using the disclosed techniques for characterizing a thermostable polymerase (the enzyme of Comb), and thus there would be no reason to modify the teachings of these references to use a different technique. The Federal Circuit case, *Winner v. Wang*, states that in order to find a motivation to modify a reference, there must be some deficiency or

problem perceived with the prior art reference. 53 U.S.P.Q.2d 1580, 1587 (Fed. Cir. 2000) (stating “there was no apparent disadvantage to the dead-bolt mechanism of Johnson, and therefore the motivation to combine would not stem from the “nature of the problem” facing one of ordinary skill in the art, because no “problem” was perceived). Comb was interested in characterizing a single, novel thermostable polymerase, not developing superior methods for assaying for enzyme activities. Utilizing the techniques described in Massey for this purpose would have been unduly burdensome and unnecessary and at no point does Comb indicate a need for a superior method of characterizing an enzyme. Moreover, one skilled in the art would fail to see the need for the elaborate techniques described in Massey to perform a routine characterization of an enzyme. Thus, there is no motivation to combine Comb with Massey as no problem with the Comb techniques was perceived.

Moreover, Applicants respectfully disagree with the Examiner’s characterization of Massey. The Examiner states that Massey “teach[es] a method of claims 45-46, 50, of assaying for an activity that modifies the rate of joining that joins (binds) a first substrate (an assay-performance substance) and a second substrate (a functionalized graphic nanotube) to form a product (binding complex) . . . .” Office Action, page 8. The Examiner cites col. 13, lines 20-22 and 44-45 as support for this proposition. *Id.* Massey describes the direct binding of an analyte of interest to a “functionalized, graphitic nanotube.” It does not describe nor suggest the use of this assay to measure an enzymatic activity for joining two substrates together. Applicants believe that the Examiner is equating binding to the enzymatic joining reaction described in the instant application. In a binding assay, there is no third substance performing the joining

activity, which is absolutely required in an assay designed to measure an enzyme activity that joins two substrates. Further, an enzyme is catalytic in nature, and thus, does not form part of a complex, unlike the nanotube or assay-performance substance of Massey as cited at col. 13. Since, claims 45-46 and 50 of the instant application require that the invention assay for an enzyme that joins two substrates, there is no reason why one skilled in the art would be motivated to combine Comb with Massey.

Consequently, the claims are not obvious over Comb in view of Massey.

Applicants respectfully request that this rejection be withdrawn.

#### **B. Rejection over Sivaraja and Massey**

The Examiner also rejects claims 55-67, 69, and 83-87 under 35 U.S.C. § 103(a) as allegedly being obvious over Sivaraja in view of Massey. Office Action, pages 7-10. The Examiner alleges that Sivaraja “teaches a method for assaying a sample for enzyme activity (DNA helicase) that cleaves a substrate (nucleic acid fragment).” *Id.* at 7. Moreover, the Examiner states that Massey teaches “measuring said enzyme activity using a luminescent label immobilized on an electrode and measuring the emitted luminescence as an indication of said enzyme activity.” Office Action, page 8.

As with Comb, Sivaraja specifically discloses affirmatively adding the helicase enzyme and specific potential modulators to the assay. See, for example, Example 1 and col. 12, line 56 to col. 14, line 33. In the single example, for instance, Sivaraja discloses using 5 nanograms of the NS3 helicase added to a 20 microliter assay buffer. Col. 16, lines 57-59. Sivaraja does not, however, describe assaying a sample for an enzyme or a factor that affects the activity of the enzyme, where it is not known whether the enzyme or factor is present in the sample or at what concentration or activity. Thus,

Sivaraja is missing a key element of the claims. Similarly, Massey does not disclose an assay for a cleaving enzyme or a factor that affects the activity of the cleavage enzyme, where it is not known whether the cleavage enzyme or factor is present in the sample or at what concentration or activity.

Sivaraja teaches using conventional assays to measure the activity of a helicase or a helicase in the presence of modulators of its activity. It does not teach the use of an electrochemiluminescent assay as claimed in the instant application. In addition, like Comb, there is no motivation to combine Sivaraja with Massey as no problem with the Sivaraja techniques was perceived. See *Winner v. Wang*, 53 U.S.P.Q.2d at 1587.

Moreover, Applicants respectfully disagree with the Examiner's characterization of Massey. Massey describes the use of graphite nanotubes, i.e, carbon, as solid supports for electrochemiluminescence assays. See, for example, Abstract. Claims 55-67, 69, and 83-87 of the instant application clearly specify that the electrode is "not a carbon electrode." Thus, neither Sivaraja nor Massey, teach the use of a non-carbon electrode for assaying a sample for a cleavage enzyme.

Moreover, in rejecting the instant application over Sivaraja in view of Massey, the Office states that Massey "teach[es] a method of claims 45-46, 50, of assaying for an activity that modifies the rate of joining that joins (binds) a first substrate (an assay-performance substance) and a second substrate (a functionalized graphic nanotube) to form a product (binding complex) . . . ." Office Action, page 8. Applicants respectfully point out that claims 45-46 and 50 were not rejected over Sivaraja in view of Massey, and consequently, the disclosure concerning a "joining" substance is irrelevant in this context. However, even if Sivaraja and Massey applied to claims 55-67, 69, and 83-87,



these claims still require a non-carbon electrode, a limitation that is not taught in either Sivaraja or Massey.

Consequently, for the aforementioned reasons, the claims are not obvious over Sivaraja in view of Massey.

For the aforementioned reasons, Applicants respectfully request that the rejections of claims 45-67, 69, and 81-87 be withdrawn.

**SUMMARY**

In view of the above amendments and remarks, Applicants submit that this application is in condition for allowance. An early and favorable action is earnestly solicited.

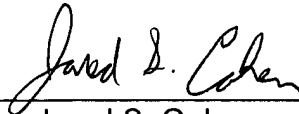
Please grant any extensions of time required to enter this amendment and response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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